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Complications, Costs, and Quality Outcomes of Patients Undergoing Cervical Deformity Surgery with Intraoperative BMP Use

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Abstract: STUDY DESIGN An epidemiological study using national administrative data from the MarketScan database. OBJECTIVE To identify the impact of bone morphogenetic protein (BMP) on postoperative outcomes in patients undergoing adult cervical deformity (ACD) surgery. SUMMARY OF BACKGROUND DATA BMP has been shown to stimulate bone growth and improve fusion rates in spine surgery. However, the impact of BMP on reoperation rates and postoperative complication rate is controversial. METHODS We queried the MarketScan database to identify patients who underwent ACD surgery from 2007-2015. Patients were stratified by BMP use in the index operation. Patients under 18 and those with any history of tumor or trauma were excluded. Baseline demographics and comorbidities, postoperative complication rates and reoperation rates were analyzed. RESULTS A total of 13,549 patients underwent primary ACD surgery, of which 1155 (8.5%) had intraoperative BMP use. The overall 90-day complication rate was 27.6% in the non-BMP cohort and 31.1% in the BMP cohort ($p < 0.05$). Patients in the BMP cohort had longer average length of stay (4.0 days vs 3.7 days, $p < 0.05$) but lower revision surgery rates at 90-days (14.5% vs 28.3%, $p < 0.05$), 6 months (14.9% vs 28.6%, $p < 0.05$), 1 year (15.7% vs 29.2%, $p < 0.05$), and 2 years (16.5% vs 29.9%, $p < 0.05$) postoperatively. BMP use was associated with higher payments throughout the 2-year follow-up period ($107,975 vs 97,620$, $p < 0.05$). When controlling for baseline group differences, BMP use independently increased the odds of postoperative complication (OR 1.22, 95% CI 1.1 - 1.4) and reduced the odds of reoperation throughout 2-years of follow-up (OR 0.49, 95% CI 0.4 - 0.6). CONCLUSIONS Intraoperative BMP use has benefits for fusion integrity in ACD surgery but is associated with increased postoperative complication rate. Spine surgeons should weigh these benefits and drawbacks to identify optimal candidates for BMP use in ACD surgery. LEVEL OF EVIDENCE 3.

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Complications, Costs, and Quality Outcomes of Patients Undergoing Cervical Deformity Surgery with Intraoperative BMP Use

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Abstract

Study Design: An epidemiological study using national administrative data from the MarketScan database.

Objective: To identify the impact of bone morphogenetic protein (BMP) on postoperative outcomes in patients undergoing adult cervical deformity (ACD) surgery.

Summary of Background Data: BMP has been shown to stimulate bone growth and improve fusion rates in spine surgery. However, the impact of BMP on reoperation rates and postoperative complication rate is controversial.

Methods: We queried the MarketScan database to identify patients who underwent ACD surgery from 2007-2015. Patients were stratified by BMP use in the index operation. Patients under 18 and those with any history of tumor or trauma were excluded. Baseline demographics and comorbidities, postoperative complication rates and reoperation rates were analyzed.

Results: A total of 13,549 patients underwent primary ACD surgery, of which 1155 (8.5%) had intraoperative BMP use. The overall 90-day complication rate was 27.6% in the non-BMP cohort and 31.1% in the BMP cohort ($p < 0.05$). Patients in the BMP cohort had longer average length of stay (4.0 days vs 3.7 days, $p < 0.05$) but lower revision surgery rates at 90-days (14.5% vs 28.3%, $p < 0.05$), 6 months (14.9% vs 28.6%, $p < 0.05$), 1 year (15.7% vs 29.2%, $p < 0.05$), and 2 years (16.5% vs 29.9%, $p < 0.05$) postoperatively. BMP use was associated with higher payments throughout the 2-year follow-up period ($107,975 vs $97,620, $p < 0.05$). When controlling for baseline group differences, BMP use independently increased the odds of postoperative complication (OR 1.22, 95% CI 1.1 – 1.4) and reduced the odds of reoperation throughout 2-years of follow-up (OR 0.49, 95% CI 0.4 – 0.6).

Conclusions: Intraoperative BMP use has benefits for fusion integrity in ACD surgery but is associated with increased postoperative complication rate. Spine surgeons should weigh these benefits and drawbacks to identify optimal candidates for BMP use in ACD surgery.

Key Words: cervical deformity; ACD; BMP; Marketscan; outcomes

Level of Evidence: 3

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Key Points

- Patients with BMP use for ACD surgery have longer length of stay, but lower rates of revision surgery
- BMP use was associated with higher payments throughout the 2-year follow-up period
- Though BMP use was associated with increased odds for developing a postoperative complication, it reduced the odds for reoperation at all time points throughout 2-years of follow-up
- Intraoperative BMP use increases fusion integrity, but these benefits must be weighed with the drawbacks

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Introduction

Cervical spinal deformity can have a significant impact on patient health related quality of life (HRQOL).[1] Though many recent publications have described the impact of corrective surgery on patients with deformities of the thoracolumbar spine, the literature surrounding cervical re-alignment is sparse.[2] High postoperative complication rates, implant failure, and need for revision remain significant concerns after these operations, with age, number of levels within the fusion construct, and baseline comorbidities having been identified as important predictors of increased postoperative morbidity.[3-6] As such, quality improvement efforts must focus on identifying clinical strategies that may improve both short- and long-term surgical outcomes.

Bone morphogenetic protein 2 (BMP-2) was first identified by Marshall Urist in 1965 as a potent osteo-inductive agent.[7] Food and Drug Administration (FDA) approval of rhBMP-2 in 2002 for single-level anterior lumbar interbody fusion (ALIF) led to an increase in its on- and off-label use for various spinal fusion procedures.[8-13] Indeed, following studies demonstrated that BMP may reduce operative time and length of stay in patients undergoing spine surgery.[10,14-18] However, there have been studies suggesting an increased risk of postoperative complications with the use of BMP.[19-22]

BMP use in spinal deformity surgery remains controversial, with studies indicating that rates of reoperation are similar with and without BMP.[23,24] However, a 2015 study

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utilizing a statewide administrative dataset found a 7.5-fold decrease in reoperations due to pseudoarthrosis with the use of BMP intraoperatively.[25] The debate regarding the risks and benefits of BMP are ongoing and the practice of individual surgeons differs considerably with regards to its utilization. Thus, we aimed to utilize a national claims dataset and provide insight into the impact of intraoperative BMP on postoperative complications, reoperations, and costs in patients undergoing cervical spinal deformity surgery.

Methods

Data Source

This study obtained a sample of the MarketScan Commercial Claims and Encounters database (Truven Health Analytics, Ann Arbor, MI) from 1/1/2007 to 12/31/2016. This database is a collection of commercial inpatient, outpatient, and pharmaceutical claims of more than 75 million employees, retirees, and dependents representing a substantial portion

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18 years of age, with a history of tumor or trauma, or who underwent single-level fusions were excluded.

Variables and Outcomes

Patients were stratified into two cohorts based on the presence (BMP group) or absence of a BMP procedure code on the index deformity surgery date (no BMP group; control), and these cohorts were mutually exclusive. Individual demographic information and comorbidity status including history of diabetes, congestive heart failure (CHF), arterial hypertension, cardiac arrhythmia, liver disease, osteoporosis, and tobacco and alcohol use of each patient were gathered. Surgical approach type (anterior, posterior, or combined) was also noted (**Table 1**).

The primary outcome of this study was the rate of reoperation following index surgery. This was measured at 90-days, 6 months, 1 year, and 2 years following admission for ACD surgery. A revision surgery was defined by the presence of the aforementioned CPT codes for deformity surgery after the index stay for the ACD surgery. A secondary outcome measure was the presence of a postoperative complication (defined as a complication occurring within 90-days of the index deformity surgery). These included pulmonary complications, acute-posthemorrhagic anemia, sepsis, central nervous system, cardiac, renal, or wound complications, deep vein thrombosis (DVT), pulmonary embolism (PE), acute kidney injury (AKI) or dysphagia (**Table 2, Table 3**).

Healthcare utilization data were also collected. Payments (stratified into physician, hospital & total payments of the index hospitalization, as well as 90-day, 6-month, 1 year, and 2 years total payments) and 90-day readmission rates were included (**Table 3**). An analysis of the BMP use over time in anteriorly corrected deformity patients was also conducted (**Figure 1).**

To isolate the impact of BMP on outcomes, a multivariate regression analysis was conducted with all significantly different baseline covariates (approach type, tobacco use). Outcomes of this analysis, with respect to complications and reoperation rate (**Table 4**). Two sample t-tests or chi-squared tests were used as appropriate. *P* values were interpreted as significant if $p < 0.05$. Information about the level of significance is provided in each table caption. Statistical analysis was conducted in R Studio version 1.0.153.

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Ethical considerations

All data from these databases are de-identified, and thus this study is exempt from IRB approval in accordance with the Health Insurance Portability and Accountability Act of 1996.

Results

Patient Cohort

A total of 13,549 patients underwent primary ACD surgery, of which 1155 (8.5%) had intraoperative BMP use. Patients who received an BMP were similarly aged (BMP: 52.1 years, non-BMP: 51.5 years, $p = 0.0710$) and in both cohorts, approximately two-thirds of patients were female. Baseline rates of CHF, hypertension, diabetes, and osteoporosis were similar between cohorts. Tobacco use was higher in the BMP cohort (33.4% vs 29.0%, $p < 0.05$). Anterior surgical approach was preferred in both cohorts, however, rates of posterior and combined surgery differed ($p < 0.05$) (**Table 1**).

Complications

The overall 90-day complication rate significantly varied between cohorts ($P < 0.05$). The complication rate was 27.6% in the non-BMP cohort and 31.1% in the BMP cohort. The specific adverse events driving this effect were deficiency and posthemorrhagic anemia, occurring 1.3x and 1.23x more frequently after BMP use ($p < 0.05$). Rates of dysphagia, DVT, PE, and wound complications were similar between the two cohorts. (**Table 2**).

Quality and health care utilization outcomes

Patients in whose ACD procedures BMP was used had longer lengths of stay (4.0 days vs 3.7 days, $p < 0.05$). The BMP cohort had significantly lower rates of revision surgeries at 90 days (14.5% vs 28.3%, $p < 0.05$), 6 months (14.9% vs 28.6%, $p < 0.05$), 1 year (15.7% vs 29.2%, $p < 0.05$), and 2 years (16.5% vs 29.9%, $p < 0.05$) following the index surgery. Costs of index hospitalization were significantly higher in the BMP cohort ($91,488 vs $80,211, $p < 0.05$). Hospital payments were individually higher in the BMP cohort ($p < 0.05$); however, physician payments were similar between BMP and non-BMP patients. Including payments

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after discharge, BMP use in patients was associated with higher payments throughout the 2-year follow-up period ($107,975 vs $97,620, $p < 0.05$) (**Table 3**).

After controlling for baseline covariates (approach type, tobacco use) in multivariate regression, BMP use independently increased the odds for developing a postoperative complication (OR 1.22, 95% CI 1.1 – 1.4). BMP use also reduced the odds for a reoperation at all time points throughout the 2 years of follow-up (OR 0.49, 95% CI 0.4 – 0.6).

The use of BMP during anterior cervical deformity correction decreased over the study period. In 2007, 13.5% of patients who underwent ACD surgery received BMP, whereas by 2015, the number was 8.5%. This measures to a -37.0% decrease in BMP use over the study period in anterior cervical deformity surgery with a particularly prominent drop in the year of 2008 (**Figure 1**).

Discussion

In 2002, BMP was approved for use in the United States by the FDA for ALIF procedures, as an alternative to iliac crest-bone grafts (ICBG).[8] Since then, studies have demonstrated that patients treated with BMP intraoperatively experience shorter operative duration, lower blood loss, shorter length of stay, lower reoperation rates, and faster returns to work than those treated with ICBG.[14,16,18] Given the complexity of adult spinal deformity cases, achieving solid arthrodesis can be quite challenging. As a result, off-label use of BMP to improve outcomes for spinal deformity cases has been of particular interest to spine surgeons.

This study utilized a large national administrative dataset to determine the impact of intraoperative BMP on postoperative complications and revision rates in patients undergoing anterior cervical deformity surgery. Though the groups of patients receiving intraoperative BMP and not receiving BMP were well matched, it is important to note that there was a higher rate of tobacco use among those patients receiving BMP treatment, a finding that may be attributed to the idea that surgeons tend to administer adjunct BMP to patients at risk for

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non-union. Despite this imbalance, we found that the revision rate was consistently higher among patients who did not receive intraoperative BMP. However, certain postoperative complications were significantly more common among patients who received adjunct BMP.

Postoperative Complications

Though the initial industry-sponsored clinical trials evaluating the use of BMP in various common spine surgery procedures demonstrated nearly no side effects, several independent studies thereafter reported adverse effects of BMP use.[20,26,27] In a study of 328,468 spinal fusion patients, BMP use was independently associated with increased the odds of any postoperative complication (OR 1.43, 95% CI 1.1 – 1.7).[28] Another study described higher rates of heterotopic ossification, infection, dysphagia, hematoma formation, and neurological deficits to be associated with BMP use in non-FDA approved spinal procedures.[29] However, these findings may vary by procedure type and surgical approach, as one study found an increased incidence of complications with BMP use in anterior cervical fusion, whereas there was no such increase for thoracolumbar or posterior cervical fusions.[30] The fear of developing a postoperative complication following cervical deformity may be the driver of decreasing BMP use over time in anteriorly corrected patients described in this study. Our study also found an increased frequency of deficiency and posthemorrhagic anemia among patients who received BMP during surgery to correct cervical spinal deformity, though other complications previously reported in other procedures that utilized intraoperative BMP (e.g. dysphagia, deep vein thrombosis, wound infection) were not significantly more frequent. (Table 2) Further, these results are particularly interesting since surgeon use of BMP would be more common in more complex deformity cases, thus leading to a difference in patient selection in the groups.

Revision Surgery

Additionally, our study assessed the effect of use of BMP on the reoperation rate after cervical deformity surgery. Many previous clinical trials have demonstrated that BMP improves the likelihood of solid fusion, which could potentially decrease the need for revision surgery.[9-12] However, the literature regarding this topic is inconclusive, with some studies finding decreased reoperation rates, and others identifying no such difference.[25,31] We discovered a significantly reduced revision surgery rate among patients treated with intraoperative BMP at 90 days postoperatively, and this effect persisted to 2 years postoperatively. Given the complexity of cervical spinal deformity cases, the risk for

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hardware failure or non-union is quite high. Thus, the ability of BMP to reduce revision by increasing chances of arthrodesis in such cases is significant. However, previous studies have demonstrated that the impact of BMP on arthrodesis is not achieved until at least 6 months postoperatively.[8,32,33] As such, the benefit to 90-day revision rates is likely due to other factors. For example, Jaeger and colleagues found that BMP had lower rates of instrumentation failure compared to autologous iliac crest bone graft for isolated L5-S1 ALIF.[34] Considering all failures were identified by the 3 month follow-up visit in this study, it is possible that the decreased revision rate at early timepoint discovered in our study is due to decreased rate of hardware failure, whereas late benefits can be attributed to higher rates of arthrodesis. We hypothesized that the reduced revision rate would lower healthcare utilization, which has traditionally reached costs upward of $100,000 postoperatively.[35,36] However, our study found that total payments remained higher among patients who received intraoperative BMP up to 2 years after the index surgery (Table 3). Spine surgeons should use their judgement in administering BMP to cervical deformity patients, weighing increased likelihood of superior fixation against the likely development of postoperative complications and increased financial burden.

Limitations

The limitations of MarketScan analyses have been previously reported by this group.[37-39] Due to the nature of the data available, potential questions and analyses are constrained by the specificity of the ICD-9 codes. For example, this study was not able to stratify by use of low vs high dose BMP. Furthermore, although only multilevel procedures were included in this study, we were unable to control for length of fusion, operative time, and blood loss -- factors which can impact postoperative complication rates. BMP may be used in situations where non-union is a concern or the surgery is more complex, and these operative characteristics were unavailable to us. However, there were significant efforts made to ensure validity of the findings. First, a relative homogenous cohort was assembled using cervical spine deformity surgery CPT codes. Nevertheless, we believe this study provides useful insight into the efficacy and safety of BMP in the surgical management of cervical spinal deformity.

Conclusion

Although the use of intraoperative BMP has demonstrated benefits in fusion integrity in ACD surgery, concern should remain with its association with increased rates of postoperative

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complications. This study identified an increased rate of postoperative complications in patients who received BMP; however, this may be confounded by increased complexity of surgery. Spine surgeons should weigh these benefits and drawbacks in identify optimal candidates of BMP use in ACD surgery.

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Figure 1. BMP Use in Anterior Deformity Correction Over Time. The percentage of anterior deformity cases from 2007-2015 that involved intraoperative BMP use (y-axis) was plotted by year (x-axis).

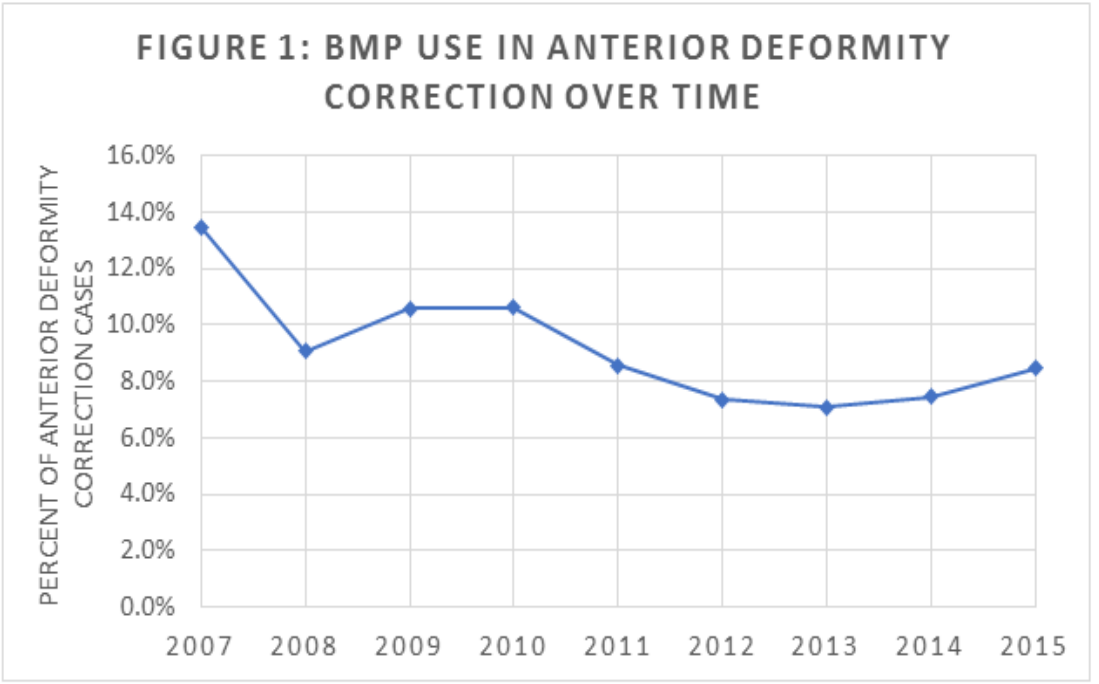

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Table 1. Demographic and Clinical Factors

Variables	Non-BMP n = 12394	BMP n = 1155	P value
Age mean (SD)	51.5	52.1	0.0710
Female N (%)	63.7	63.6	0.5300
CHF N (%)	6.1	6.5	0.6093
Hypertension N (%)	41.1	43.6	0.0952
Tobacco N (%)	29.0	33.4	**0.0015**
Diabetes N (%)	20.1	19.1	0.4372
Liver Disease N (%)	7.2	6.6	0.4135
Cardiac Arrythmias N (%)	15.7	15.8	0.8926
Osteoporosis N (%)	19.3	20.5	0.3193
Approach Type			**< 0.0001**
Anterior	84.7	89.2	
Posterior	9.0	7.7	
Circumferential	6.2	2.1	

Table 2. 90 Day Overall Complications

Variables (%)	Non-BMP n = 12394	BMP n = 1155	P value
Any complication	27.6	31.1	**0.0127**
Dysphagia	2	1.4	0.1669
Deep Vein Thrombosis	0.5	0.4	0.8669
Deficiency Anemia	9	11.6	**0.0034**
Hematoma	1.7	2.3	0.1597
Posthemorrhagic Anemia	11.9	14.7	**0.005**
Wound Dehiscence	0.9	0.6	0.3731
Wound Infection	1.9	2.5	0.1483
Stroke	1	1.6	0.0803
PE	1	0.9	0.7136

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Table 3. Quality Outcomes

Variables	Non-BMP n = 12394	BMP n = 1155	P value
Length of stay mean (SD)	3.7	4	**0.0213**
Reoperations			
90 days	28.3	14.5	**< 0.0001**
180 days	28.6	14.9	**< 0.0001**
365 days	29.2	15.7	**< 0.0001**
730 days	29.9	16.5	**< 0.0001**
Index Hospitalization Costs (mean)			
Physician Payments	$10,680	$9,791	0.0796
Hospital Payments	$62,532	$74,895	**< 0.0001**
Total Payments	$80,211	$91,488	**< 0.0001**
Total Payments (Index + Post Discharge)			
90 days	$85,838	$97,917	**< 0.0001**
365 days	$92,357	$103,270	**0.0004**
730 days	$97,620	$107,975	**0.0021**

Table 4. Multivariate Adjusted Analysis to Identify Impact of BMP on Outcomes

Variables	OR	95% CI	P value
Any complication	1.22	1.07 - 1.40	**0.0025**
Reoperations			
90 days	0.44	0.38 - 0.53	**< 0.0001**
180 days	0.46	0.38 - 0.54	**< 0.0001**
365 days	0.47	0.40 - 0.56	**< 0.0001**
730 days	0.49	0.41 - 0.57	**< 0.0001**

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